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Reduced serum homocysteine levels in type 2 diabetes

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Summary *Objective:* To assess the contribution of fasting blood glucose and methylene-tetrahydrofolate reductase (MTHFR) gene polymorphism on fasting serum homocysteine (tHcy) levels in patients with uncomplicated type 2 diabetes compared with healthy subjects.
Methods and results: We studied 105 type 2 diabetic patients without cardiovascular complications or diabetic nephropathy (55 males, 50 females, mean age 53±10 years, mean duration of diabetes 11.4±8 years) and 120 age- and sex-matched control subjects (65 males, 55 females, mean age 52±8 years). tHcy and other biochemical variables were measured. The C677T MTHFR gene polymorphism was determined by analysis of *Hin*fI restriction fragment length polymorphism tHcy levels were significantly lower in diabetic patients compared with control subjects (7.7 ± 2.2 vs. 11.8 ± 4.5 μmol/l, $P<0.0001$). In both patients and control subjects, homocysteinemia was higher in men than in women (8.4±2.6 vs. 7.3±2.0 μmol/l, $P<0.03$, and 13.0±5.3 vs. 10.4±2.6 μmol/l, $P<0.0001$, respectively). Levels were slightly higher in subjects with the mutated Val/Val genotype compared with the Ala/Val plus Ala/Ala genotypes in both diabetic patients ($P<0.02$) and control subjects ($P<0.003$). On simple regression analysis, tHcy was inversely related with blood glucose levels ($P<0.02$) and directly with sex ($P<0.04$) in diabetic patients, and with sex ($P<0.0001$), age ($P<0.02$), BMI ($P<0.03$), systolic and diastolic blood pressure ($P<0.0004$ and $P<0.0002$), uric acid and creatinine ($P<0.0001$ and $P<0.0003$) in control subjects. On multiple regression, tHcy levels were associated with sex ($P<0.03$) and glucose levels ($P<0.04$) in diabetic patients, and with uric acid ($P<0.002$) and MTHFR genotype ($P<0.03$) in control subjects.

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Conclusion: In type 2 diabetic patients without nephropathy, basal levels of tHcy were 35% lower compared with healthy controls. Chronic hyperglycemia may control tHcy by affecting its renal excretion, or accelerate hepatic trans-sulfuration secondary to insulin disorders.

Introduction

Type 2 diabetes mellitus is characterized by a high incidence of vascular complications [1]. Cardiovascular complications are the leading cause of death in type 2 diabetes mellitus. Many factors, such as hyperglycemia, dyslipidemia, and abnormalities in hemostasis, are implicated in the development of diabetic macroangiopathy [2]. In recent years fasting serum homocysteine (tHcy) levels have emerged as an independent risk factor for the development of atherosclerosis [3—5]. Subjects with genetically inherited severe hyperhomocysteinemia and homocystinuria are affected by atherothrombotic complications at an early age [5]. Severe hyperhomocystenemia is caused by rare inborn errors of homocysteine metabolism involving enzymes such as cystathionine β-synthase. Mild hyperhomocysteinemia may be due to the presence of a thermolabile isoform of the enzyme 5,10 methylene-tetrahydrofolate reductase (MTHFR), a condition caused by an alanine-to-valine substitution in the protein sequence. The relative frequency of homozygotes for the mutation ranges from 5 to 15% among populations; considerable evidence indicates that it represents an independent risk factor for atherosclerosis in the coronary, cerebral, and peripheral vessels [5]. In general, interindividual variation in tHcy levels is regulated by the interaction of genetic and nutritional factors, in which dietary habits, such as the intake of vitamins (folic acid, vitamin B6 and B12), play an important role [6].

The relation between diabetes and tHcy levels is still unclear. There is general consensus that tHcy levels in the fasting state are not elevated in diabetics without complications whereas levels after methionine load may be elevated in some [7—9]. Several studies have suggested a role for renal function in reducing the clearance of tHcy [10,11].

The aim of the present study was to assess the possible contribution of blood glucose levels and MTHFR polymorphism on tHcy circulating levels in type 2 diabetic patients without diabetic nephropathy and/or cardiovascular complications.

Methods

The study population consisted of 105 subjects with type 2 diabetes (Table 1) recruited from an outpatient Diabetes Clinic. One hundred twenty healthy volunteers, recruited from the same geographic area and matched for demographic variables (age, gender) with the diabetic population, served as a control group. History of coronary disease and/or cerebrovascular accidents, liver or kidney dysfunction, diabetic proliferative retinopathy, or neoplastic disease, vitamins supplementation, were considered as exclusion criteria. Only subjects with normal urinary albumin excretion (<30 mg/24 h), were included in the study. Urinary albumin concentration was analyzed by an automated nephelometric enzyme-linked immunosorbent assay (Behringwerke AG, Marburg, Germany). All participants gave their informed

Table 1 Demographic and metabolic variables in type 2 diabetic patients and healthy control subjects

	Diabetics	Controls	*P*
n	105	120	
M/F	55/50	65/55	n.s.
Age (years)	53±10	52±8	n.s.
Duration of diabetes (years)	11.4±8.0	—	—
Current smokers (%)	30	25	n.s.
BMI (kg/m^2)	28.8±5.3	24.0±4.8	0.001
SBP (mmHg)	135±12	124.5±11	0.001
Total cholesterol (mmol/l)	5.15±1.2	5.09±1.1	n.s.
HDL cholesterol (mmol/l)	1.20±0.4	1.32±0.4	0.03
Triglycerides (mmol/l)	1.62±1.0	1.23±0.9	0.001
Glucose (mmol/l)	10.4±4.5	5.2±0.5	0.001
HbA_{1c} (%)	8.0±1.5	—	—
Creatinine (mmol/l)	79±12	78±11	n.s.
Creatinine clearance (ml/min)	87±25	93±25	n.s.
Uric acid (mmol/l)	253±70	229±73	0.02
Folate (nmol/l)	11.2±3.9	11.0±4.1	n.s.
Vitamin B12 (pmol/l)	394±192	376±190	n.s.
Total Hcy (mmol/l)	7.7±2.2	11.8±4.5	0.001

Data are mean±SD.